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Review

Evidence for Genetic Relationships in Attention-Deficit Hyperactivity Disorder

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a common disorder in the world. The main topics of the disorder that are seen in the world and counted as markers in this regard and that adversely affect social life are behavioral disorders and mental disorders underlying hyperactivity. Attention-deficit hyperactivity disorder, which is associated with hyperactivity among the public and is considered one of the main conditions, is the most common. If it is not treated and controlled, it will lead to psychiatric and social disorders and can become permanent. It is one of the most important disorders in child and adolescent psychiatry due to reasons such as developmental differences from preschool to adulthood. In 3–50% of people with ADHD, which starts in childhood, symptoms continue into adulthood. Anxiety disorder, an inability to control anger, sudden ups and downs in emotions and mood disorders, a desire to use substances, and personality deterioration are all common comorbidities in people with ADHD. At the same time, it can be said that ADHD has the effect of many genes that are moderately and highly effective and mediate this disorder. In addition to being encountered so often, there is no exact information about ADHD. In this review, the symptoms of ADHD, its relationship with genes, and the psychiatric disorders that may accompany it will be reviewed within the framework of previous research and studies and will be attempted to be summarized in perspective.

Keywords: ADHD, antisocial behavior, genetic relationship, hyperactivity, psychiatric disorders

Hyperactivity is defined as acting out of character, having unusual mobility, or being overly active. It is a psychological disorder that people with this condition cannot control on their own. Attention-deficit hyperactivity disorder (ADHD) occurs in people with hyperactivity disorder.[1] This is originating the person cannot concentrate his or her attention in an area or has difficulty standing still in a place. The disorder begins in childhood and lasts a lifetime. Behavioral symptoms such as hyperactivity and impulsivity are characterized by significant morbidity and disability caused by these symptoms. It is a neuropsychiatric disorder that seriously disrupts order by causing problems in home, work, and school life for people who experience it. This disorder generally decreases with age. According to the diagnostic and statistical manual of mental disorders (DSM-IV) diagnostic criteria, the prevalence of ADHD is around 8% in childhood, 6% in adolescence, and 4% in adulthood.[2] Although it is the most commonly diagnosed psychiatric disorder in children, its onset generally occurs around the age of three but is introduced in the primary school years, where attention span and concentration are expected during the learning period, which requires regularity and focuses to be diagnosed. The findings of research on the prevalence of ADHD, particularly in terms of case interpretation, may differ.[3] According to the data, the incidence of ADHD in adults is lower than expected. Although there is no definitive opinion on the research, many studies have shown that neurobiological and genetic factors play an important role in the development of the disorder, which is a heterogeneous disorder with unknown causes.[4] Among the reasons for the occurrence of this disorder, organic and social causes stand out. In addition to this condition, it accompanies the diagnosis of ADHD in many other psychiatric disorders. According to research, at least 65-89% of adult patients diagnosed with ADHD have one

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or more other psychiatric disorders.[5] It is likely to be multifactorial. It is likely to be different from the other in each case. In other words, each phenomenon may be due to a different cause than the other, or it may be due to a different factor in the same phenomenon. The most common comorbidities with the diagnosis of ADHD are mood and anxiety disorders, as well as personality disorders and substance use disorders.[6] The coexistence of multiple psychiatric disorders worsens the clinical picture in terms of disorder treatment and outcome. The main cause of this deterioration is a social disability, risky behaviors, and the accompanying decreased quality of life. These behaviors are important elements that should be considered and emphasized throughout the disorder process. As we focus on the diagnosis of ADHD, the diagnosis is explained with different concepts. It is thought to have occurred as a result of "damage to the brain" as a result of the sources obtained from the results of research conducted on children suffering from encephalitis after the epidemics in 1917 and 1918. It was determined by 1947 that children with extreme mobility, inability to focus, confusion, impulsivity, perseverance (the repetition of a movement, word, or behavior with associated emotions), and cognitive disability had brain damage that could not be demonstrated later.[7] This condition has been recorded as "minimal brain damage syndrome." Some clinicians who do not defend this idea have argued that unless there is any damage to the brain, they cannot conclude that it is a brain injury. Later, in the 1960s, "minimal brain damage" was diagnosed and used for a group of children with poor coordination, problems with learning, and emotional ups and downs but without a specific neurological disorder. Attention-deficit hyperactivity disorder was defined as an attention deficit in 1983 and tried to be explained in 1992 with concepts such as a weak disabling process. Recently, research has been more geared towards revealing genetics, brain imaging, neurochemical changes, and psychosocial causes. According to the accepted opinion, ADHD is a common symptom of different pathologies.[8]

The number of behavioral symptoms that can occur in an organism is limited. Fragile X syndrome (genetic overload), central nervous system infections (people whose immune systems are under more pressure due to socio-economic reasons), fetal alcohol syndrome, lead poisoning, widespread resistance of the body to thyroid hormone, children with very low birth weight (trauma that occurs before or after birth), and a wide range of disorders that may occur in the brain due to other factors can ultimately cause similar behavioral responses.[9] There are clinical conditions in which we know that the symptoms of ADHD are present. In addition, although a single hypothesis is not accepted when the facts are examined in the etiology of ADHD, many proofs support most of the hypotheses and are evidence. As we have noted, the majority of hypotheses on this subject focus on genetics, birth, or postpartum disorders that develop due to various reasons and occur in brain function. Furthermore, it was determined that socialization was dependent on the data gathered.[10] All hypotheses are supported by a slightly higher incidence in people with low socioeconomic status, poor living conditions, and neglect or abuse, as evidenced by children in orphanages having shorter attention spans over time and is observed to be in an excessive mobility state.[11] The main reason for this was determined by the child's prolonged sensory deprivation and the improvement of the situation, such as the child's adoption.

NEUROBIOLOGY OF ADHD

The importance of the functions of dopamine (DA) and noradrenaline (NA) synthesized from the DA molecule in other cognitive functions such as gathering attention, concentrating, establishing motivation, and performing the state of wakefulness is seen. According to the results of the studies, it was seen that children with minimal brain damage could see the most disruption in DA, serotonin, and NA metabolism.[12] To prove the existence of this condition, when individuals with ADHD are given methylphenidate, d-amphetamine, and pemoline, which are stimulants of the central nervous system that will increase the levels of DA and NA in their brains, and at the same time antidepressants are given, the result obtained is evidence of the disorder in catecholamine metabolism.[13] Given stimuli, catecholamine release increases. This minimizes its buyback. As a result of the research, tricyclic antidepressant drugs, and monoamine oxidase inhibitors also reduce hyperactivity and minimize the symptoms seen.[14] However, it is difficult to make a definitive judgment yet, and no single responsible neurotransmitter has come to the fore. In animal experiments, it has been seen that it will cause ADHD after the use of DA and NA. This is because hyperactive and impulsive behaviors are exhibited in experimental animals, and disorders in the catecholamine system appear.[14] At the same time, DA is thought to have significant efficacy in the operant reward mechanism, which appears to be problematic in ADHD and has

been observed not to work in attention deficit. In addition, some studies have suggested that estrogen has a role in hyperactivity disorder and thus may be responsible for the gender differences that can be seen in the symptoms of ADHD. To summarize, the metabolism of DA and NA can be attributed to a significant reduction in ADHD. However, it is worth noting that this is not based on the assumption that there is a single dopaminergic system. It can be said that the reason for this is the interaction between the serotonin and catecholamine systems.[15]

GENETIC FACTORS

It has also been observed that children with ADHD based on genetic factors are frequently encountered in their first-degree blood relatives. Monozygotic twins have a higher risk of synapses than synods, and siblings of hyperactive children have twice the risk as the general population. In the family studies conducted using the clinical data obtained, it was found that the risk of ADHD in the mothers and fathers of children with ADHD was two to eight times higher. According to research, the genetic transmission rate of people with ADHD is estimated at 80%. Based on these data, it has been revealed that genetic factors are very important in ADHD. Studies are ongoing on genes that cause impaired metabolism of neurotransmitters (catecholamines and possibly serotonin), which play an important role in the neurobiology of ADHD. The results are difficult to attribute with certainty and seem to take a long time. This is because ADHD occurs when more than one gene is combined, as in other psychiatric disorders.[16]

Thyroid Hormone Receptor Gene

Hauser and his colleagues[17] discovered a link between ADHD and a mutation in the thyroid hormone receptor beta gene on the third chromosome in 1993. As a result of the realization of this mutation, which is the dominant transition of autosomal (a group of chromosomes without sex chromosomes) chromosomes in research, general resistance to thyroid hormone occurs in the human body. Around 42% of adult patients with extreme resistance to this thyroid hormone are diagnosed with ADHD. Then, in the research conducted on the subject, a relationship was found between the levels of hyperactivity and impulsivity and thyroid hormone levels. However, no link has been found between the condition and patients' attention deficit.[17]

Dopamine Receptor Genes

Dopamine is a chemical that is naturally produced in the bodies of humans and animals and is found in the body in that way. It is a neurochemical that is important for the realization of many processes belonging to the brain. The effect can sometimes be inhibitory and sometimes exclusive. In brain activity, they act as neurotransmitters (chemicals that enable communication between neurons or between neurons and another type of cell, carrying brain activity through the nervous system through neural signals) by activating DA receptors.[18] In addition, DA is the name of the region of the forebrain in the hypothalamus that, when viewed anatomically, is located under the thalamus and forms the floor of the third ventricle, the heart ventricle. In addition, one of the most important tasks of this section, which consists of small nuclei, is to establish the connection between the brain's endocrine system through the pituitary gland and the hormones secreted and mixed into the blood that function as a neurohormone. This neurohormone suppresses the secretion of prolactin (an internal secretory hormone) in the frontal lobe of the pituitary (an endocrine gland) by attaching to receptors such as D1, D2, D3, D4, D5, D6, D7, and TAAR1.[19] It is encoded in humans by the prolactin (PRL) gene. Its synthesis is made by "dopaminergic" cells located in the substantia nigra (known as "dark matter," a basal ganglion structure located in the midline of the brain that plays a major role in the mechanism of movement and reward). This allows sleep, pleasure, motor movements, and learning to take place and be effective in the body. Antipsychotic drugs, that is, neuroleptic drugs, are used in the treatment of psychoses, especially schizophrenia, by acting on the DA D2 receptor. Due to the effects of these drugs on the sympathetic nervous system, after their use, blood pressure rises and the heartbeat accelerates. The amount of DA is increased by the 3,4-dihydroxy-L-phenylalanine (L-DOPA) molecule.[20] L-DOPA is a DA precursor found in amino acid form. It functions in the body and brain by converting DA. Thus, by crossing the blood-brain barrier, it acts on Parkinson's and dopa-sensitive dystonia (an involuntary movement disorder in the muscles).[20]

DRD2, DRD4, DRD5 Genes

A 1991 study found that the A1 allele of the dopamine D2 receptor (DRD2) gene has an important role in ADHD. As a result of the research, ADHD is an important candidate gene in the catecholaminergic system regulation disorder.[21]

The dopamine D4 receptor (DRD4) gene is located on chromosome 11, and the seven repeat alleles of this gene are the most working genes in ADHD. The possibility of a link between hyperactivity and DRD4 has also been proven in mouse studies. The study showed that when the DRD4 receptor gene in mice was blocked, DA synthesis in the dorsal striatum increased. The result of this was a reduction in novelty-seeking behaviors in mice. Thus, the existence of a relationship between human DRD4 and novelty seeking was supported. As evidence of this, a 2001 meta-analysis by Faraone et al.[16] on this subject proved a small but statistically significant relationship between ADHD and DRD4 seven repetition alleles as a result of eight case-control studies and fourteen family-based approaches and post-study evaluations.[22]

The dopamine D5 receptor (DRD5) is located on the fourth chromosome. Although studies of this gene with 148 bp alleles are ongoing, a definite and clear conclusion has not yet been reached.[23]

Dopamine Transporter Gene

The dopamine transporter 1 (DAT-1) gene is located on the fifth chromosome. In this gene, 10 repeat alleles of 480 bp are controlled. When the studies and evaluations made in this field over time are examined and taken into consideration, it is seen that there is a statistically acceptable concentration in the genetics of the dopaminergic system. Compared to this, NA, which is synthesized from DA, is very important in hyperactivity disorder, especially in waking, visual attention, learning, and executive functions.[24] To summarize, the genes that attract the most attention and are emphasized in the genes examined in ADHD and at the same time have positive and statistically significant findings can be stated as DRD4 and DAT1.[25] It should be taken into consideration that the studies on this subject are still ongoing and a clear conclusion has not yet been reached. If we conclude, it can be said that many genes with moderate and high levels of influence have an effect on ADHD and are mediators for this disorder.[26]

Also, studies and experiments have shown that multiple factors that occur as a result of N-methyl D-aspartate receptor subunit 2B (GRIN2B) gene variants, lysine(K)-specific demethylase 6B (KDM6B) mutations, and Src homology 3 domain and ankyrin repeat-containing (Shank), serotonin 1B receptor gene (HTR1B) and genes encoding the synaptic vesicle regulatory protein called Synaptosomal associated protein 25 kDa (snap-25) cause ADHD disorder.[27-30] Accordingly, in some cases, the effect of genes is little or nonexistent. This is due to negative environmental factors.

In conclusion, 5% of hyperactivity cases are thought to be neurological disorders. It is also suggested that it is caused by an inability to let go of unpleasant memories and emotions. Therefore the relatively consistent evidence shows that ADHD is caused by genetic, biological, and psychosocial factors, with multiple causes, including brain damage, and as a result, ADHD. At the same time, it can be said that conditions such as depression, substance abuse, and obesity that occur before and after ADHD are often seen in the clinical picture. However, until now, the exact mechanisms of action and effects of ADHD were not been fully known. In addition, despite the high degree of effectiveness of drugs used for ADHD, these treatment methods do not appear to be curative. As a result, more than one stimulant and the non-stimulant drug has been approved and presented for use in the regression and long-term treatment of ADHD, which frequently causes emotional ups and downs, excessive anxiety, awkward behavior, difficulty learning, and a proclivity for substance use. According to research, while ADHD is seen in two-thirds of adolescence, the destructive symptoms of ADHD persist into adulthood. Therefore, it has been determined that people with ADHD have a risk of developing a wide range of functional disorders. It can be said that the treatment process is very time-consuming as a result of the fact that effectiveness varies greatly between individuals and patients, making it difficult to choose the existing agents for the treatment to be applied and, at the same time, determine the most effective and useful ADHD drug for a particular patient to be treated. When the drug that treats or may treat ADHD targets dopaminergic and noradrenergic transmission, if the results of multiple studies, research, and experiments are examined, it is often caused by the disruption of more than one gene, while in rare cases, a single gene is responsible. These are the products of the coexistence of many genes (the thyroid receptor gene), many of which are of low influence. To eliminate the negative effects of ADHD on functionality and interpersonal relationships, it is necessary to start the necessary preventive and therapeutic interventions at a very early stage. With thyroid hormone replacement being used for the treatment of ADHD caused by a mutation in the thyroid receptor gene, it was seen after research that the patient improved and some of the behavioral symptoms were reduced. As a result of this data, it was thought that mutant thyroid

receptors may be responsible for some of the people with a genetic predisposition to ADHD. It has been seen that more than one gene with a moderate effect that causes ADHD can be effective and interact. Noradrenaline, synthesized by DA, has proven to be important in ADHD, including wakefulness, visual distraction, inability to focus, all kinds of learning, and executive functions. We know that it will be difficult to analyze the genetic makeup of ADHD. However, the technological advances used in the studies are making great progress. In the studies that have been or will be done in the next 10-15 years, we will obtain more genomic, transcriptomic, and epigenomic data. Thus, we will have reached better the right brain structure and function. In addition, we will be prepared to discuss the etiology of ADHD and the advances that will be made to diagnose and treat the disorder. When ADHD is examined, it has been seen to be one of the most inherited psychiatric disorders, and researchers are investigating the underlying genes of the disorder to lead to better treatments by focusing on gene discovery as a disorder.

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REFERENCES

1. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016 Mar 19;387:1240-50.
2. Hunt TKA, Slack KS, Berger LM. Adverse childhood experiences and behavioral problems in middle childhood. Child Abuse Negl. 2017 May;67:391-402.
3. Häge A, Hohmann S, Millenet S, Banaschewski T. [Attention deficit hyperactivity disorder in childhood and adolescence : Current state of research]. Nervenarzt. 2020 Jul;91:599-603.
4. Leffa DT, Caye A, Rohde LA. ADHD in Children and Adults: Diagnosis and Prognosis. Curr Top Behav Neurosci. 2022;57:1-18.
5. Wolraich ML, Hagan JF, Allan C, Chan E, Davison D, Earls M, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/ Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019 Oct;144:e20192528.
6. McLoughlin G, Ronald A, Kuntsi J, Asherson P, Plomin R. Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive-impulsive components. J Abnorm Child Psychol. 2007 Dec;35:999-1008.
7. Başkaya E, Memişoğlu M, Erbaş O. Fructose Consumption Effect on Bipolar and Attention Deficit Hyperactivity Disorder. JEB Med Sci 2021;2:27-33.
8. Smits M, Dippel DW, Houston GC, Wielopolski PA, Koudstaal PJ, Hunink MG, et al. Postconcussion syndrome after minor head injury: brain activation of working memory and attention. Hum Brain Mapp. 2009 Sep;30:2789-803.
9. Nikolas MA, Burt SA. Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: a meta-analysis. J Abnorm Psychol. 2010 Feb;119:1-17.
10. Aybüke Yayla M, Arda B, Çağlar Ö, Erbaş O. Peptide Hormones and Neurodegenerative Diseases. JEB Med Sci 2021;2:62-75.
11. Saccaro LF, Schilliger Z, Perroud N, Piguet C. Inflammation, Anxiety, and Stress in Attention-Deficit/Hyperactivity Disorder. Biomedicines. 2021 Sep 24;9:1313.
12. Frank MJ, Santamaria A, O'Reilly RC, Willcutt E. Testing computational models of dopamine and noradrenaline dysfunction in attention deficit/hyperactivity disorder. Neuropsychopharmacology. 2007 Jul;32:1583-99.
13. Prince J. Catecholamine dysfunction in attention-deficit/hyperactivity disorder: an update. J Clin Psychopharmacol. 2008 Jun;28:S39-45.
14. Otasowie J, Castells X, Ehimare UP, Smith CH. Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database Syst Rev. 2014 Sep 19;:CD006997.
15. Bergamini G, Mechtersheimer J, Azzinnari D, Sigrist H, Buerge M, Dallmann R, et al. Chronic social stress induces peripheral and central immune activation, blunted mesolimbic dopamine function, and reduced reward-directed behaviour in mice. Neurobiol Stress. 2018 Feb;8:42-56.
16. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005 Jun 1;57:1313-23.
17. Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, Mixson AJ, et al. Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. N Engl J Med. 1993 Apr 8;328:997-1001.
18. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. Physiol Rev. 1998 Jan;78:189-225.
19. Uyanikgil Y, Özkeşkek K, Çavuşoğlu T, Solmaz V, Tümer MK, Erbas O. Positive effects of ceftriaxone on pentylenetetrazol-induced convulsion model in rats. Int J Neurosci. 2016;126:70-5.
20. Darmopil S, Martín AB, De Diego IR, Ares S, Moratalla R. Genetic inactivation of dopamine D1 but not D2 receptors inhibits L-DOPA-induced dyskinesia and histone activation. Biol Psychiatry. 2009 Sep 15;66:603-13.
21. Erbaş O, Akseki HS, Aktuğ H, Taşkıran D. Low-grade chronic inflammation induces behavioral stereotypy in rats. Metab Brain Dis. 2015 Jun;30:739-46.

22. Gornick MC, Addington A, Shaw P, Bobb AJ, Sharp W, Greenstein D, et al. Association of the dopamine receptor D4 (DRD4) gene 7-repeat allele with children with attention-deficit/hyperactivity disorder (ADHD): an update. Am J Med Genet B Neuropsychiatr Genet. 2007 Apr 5;144B:379-82.
23. Barr CL, Wigg KG, Feng Y, Zai G, Malone M, Roberts W, et al. Attention-deficit hyperactivity disorder and the gene for the dopamine D5 receptor. Mol Psychiatry. 2000 Sep;5:548-51.
24. Krause J, Dresel SH, Krause KH, La Fougère C, Zill P, Ackenheil M. Striatal dopamine transporter availability and DAT-1 gene in adults with ADHD: no higher DAT availability in patients with homozygosity for the 10-repeat allele. World J Biol Psychiatry. 2006;7:152-7.
25. Turic D, Swanson J, Sonuga-Barke E. DRD4 and DAT1 in ADHD: Functional neurobiology to pharmacogenetics. Pharmgenomics Pers Med. 2010;3:61-78.
26. Chang S, Yang L, Wang Y, Faraone SV. Shared polygenic risk for ADHD, executive dysfunction and other psychiatric disorders. Transl Psychiatry. 2020 Jun 9;10:182.
27. Myers SJ, Yuan H, Kang JQ, Tan FCK, Traynelis SF, Low CM. Distinct roles of GRIN2A and GRIN2B variants in neurological conditions. F1000Res. 2019 Nov 20;8:F1000 Faculty Rev-1940.
28. Gao Y, Aljazi MB, He J. Kdm6b Haploinsufficiency Causes ASD/ADHD-Like Behavioral Deficits in Mice. Front Behav Neurosci. 2022 May 31;16:905783.
29. Ma SL, Chen LH, Lee CC, Lai KYC, Hung SF, Tang CP, et al. Genetic Overlap Between Attention Deficit/ Hyperactivity Disorder and Autism Spectrum Disorder in SHANK2 Gene. Front Neurosci. 2021 Apr 27;15:649588.
30. Najera K, Fagan BM, Thompson PM. SNAP-25 in Major Psychiatric Disorders: A Review. Neuroscience. 2019 Nov 10;420:79-85.